Remarks/Arguments

I. INTERVIEW SUMMARY

On December 16, 2009, Examiner Brian Gangle and the undersigned representative Valerie Neymeyer-Tynkov discussed the above-identified application by telephone. During the interview, the rejection of claims 82-84 under 35 U.S.C. 112 as not enabled was discussed.

As indicated in the Examiner's Interview Summary dated December 18, 2009, during the interview, it was noted that the focus of the present invention is the delivery of antigens as vaccines, rather than the antigens themselves.

In observance of USPTO rules, Applicant's representative further notes herebelow the general thrust of discussion presented to the Examiner. During the interview, claims 82-84 were discussed in the context of the 112 enablement rejection mentioned above. Mrs. Neymeyer-Tynkov noted that the present application discloses it is difficult for antigens, particularly large antigens, to penetrate the skin, because the skin provides a barrier that precludes the uptake of antigens (see e.g. page 2, top). As a general rule, the exposure of large antigenic molecules on the skin requires a large load of molecules but provides a very weak immune response. In the present invention, penetrants are able to pass through the skin through intercellular spaces or pores, carrying antigens through the barrier so they may, for instance, induce a protective immune response. The focus of the invention is that the penetrants can deliver the antigen across the barrier, rather than the specific makeup of a given antigen.

In the Interview Summary, the Examiner also states that the weight of intended use in terms of enablement versus prior art was discussed. The general thrust of discussion in this regard was that the term "vaccine" implies an intended use that has patentable weight where a composition is novel over the prior art.

Applicant and Applicant's representative thank the Examiner for his time and efforts in discussing the application.

II. RESPONSE TO OFFICE ACTION

In the Claims

No new matter is believed to be added by this Amendment. Support for changes to the claims and for new claims may be found throughout the application as filed.

Claims 80-88 all read on the species elected in response to the Office Action issued September 15, 2005 in this application.

Response to new rejections under 35 U.S.C. §112:

Rejection of Claims 82-84:

In the present Action, claims 82-84 are rejected as lacking enablement under 35 USC 112. Specifically, the rejection states that the specification is enabling for compositions providing a protective response against tetanus comprising tetanus toxoid (TT) as an antigen, but does not reasonably enable protective immune response against any given disease comprising any given antigen.

In response, Applicant submits, as indicated in the above Interview Summary, that the focus of the present invention is the delivery of antigens rather than makeup of a specific antigen. The present invention, via the claimed penetrant, allows the delivery of TT as well as other antigens across the skin's barrier (in particular, the epidermal stratum corneum) to provide e.g. a protective immune response.

See for instance page 21 lines 1-3 and page 17 line 32 to page 18 line 14 of the application as filed, disclosing that antigen is transported across the skin's barrier in the form of a physical or chemical complex with the penetrant, and that penetrants associated with antigens can elicit a therapeutic or prophylactic immune response. See also page 2 lines 1-10, disclosing the barrier provided by the stratum corneum, particularly to large macromolecules, and page 6 line 24 to page 7 line 16, disclosing that vaccines of the present invention penetrate the stratum corneum via virtual channels or pores between corneocytes, and carry antigens through without greatly perturbing the skin.

See also, page 14 lines 5-28 of the application as filed, discussing the mechanism by which delivery is believed to be achieved. Applicnat discloses that a penetrant of the present invention penetrates the stratum corneum by adapting to the barrier's confining pores and possibly decreasing barrier resistance (via pore widening pores or channel opening). The application expressly notes that penetration is different from permeation, which depends on basic diffusion principles (e.g. a penetrant or antigen concentration gradient). The mechanism of delivery of an antigen does not rely on specific characteristics of TT, but rather may be used to deliver other antigens

At least in view of the foregoing, Applicant respectfully submits that the skilled person would understand that the present invention is directed to the delivery of antigens in general, so they may provide e.g. a protective response, and not limited to the delivery of TT or any other one antigen. Applicant respectfully requests that this rejection be withdrawn therefore.

Rejection of Claim 60:

In the present Action, the term "the irritant" in claim 60 is rejected as indefinite for failure to provide antecedant basis. In response, Applicant respectfully submits that pending claim 60 now properly depends from claim 37, and requests that this rejection be withdrawn.

Response to rejection under 35 U.S.C. §102(b):

In the present Action, claims 37, 38, 40-41, 58-59, 65, 80-82 and 84 are rejected under 35 U.S.C. §102(b) as anticipated by Paul et al. (Vaccine Res. 4:145-164 (1995)). The rejection states that Paul discloses a transdermal carrier comprising ethanolic soybean phosphatidylcholine, sodium cholate, and lipid A (which includes cytokine activity) which is associated with an antigen (purified BSA, an allergen).

With regard to the rejection of claim 37, currently amended, Applicant respectfully notes that pending claim 37 requires 4 distinct elements: (in part) (a) a carrier comprising a penetrant formed of a fluid droplet surrounded by a coating of at least 2 substances, (b) a compound which specifically has or induces cytokine or anti-cytokine activity, (c) antigen/allergen and (d) chemical irritant/derivative or

pathogen/derivative. Applicant respectfully submits that the sodium cholate and triethanolamine referred to as chemical irritants in the present rejection are part of element (a), not element (d), and requests that this rejection be withdrawn therefore.

The bottom of page 3 to top page 4 of the present Action state that Paul et al. page 148 discloses using sodium cholate and triethanolamine to prepare transfersomes (first paragraph under heading "Transfersomes preparation"), and that sodium cholate and triethanolamine are chemical irritants or derivatives thereof. Applicant respectfully submits that the chemicals mentioned in the rejection are expressly part of transfersomes used in Paul (corresponding to element (a) of claim 37). However, claim 37 and page 23, 4th full paragraph, of the present application state in part that the present invention further comprises a chemical irritant or compound from a pathogen (emphasis added). Element (d) is indicated as a separate element to show that, in addition to elements (a), (b) and (c), a chemical irritant (d) or other chemical mentioned in element (d) is part of the claim 37 composition.

Applicant notes that the teachings of Paul indicate that no chemical irritant, such as a permeation enhancer, is added to its compositions. See for intance Paul page 147 lines 4-7, expressly disclosing that known methods for transporting molecules across the skin barrier include adding chemicals such as alcohols, azones and surfactants to increase skin permeability. See also Paul page 163, 2nd paragraph, stating that Paul's results with transfersomes are "inexplicable" within the framework of the classical skin penetration enhancement model. Paul's compositions do not use chemicals accepted in the state of the art to increase delivery across the skin barrier; i.e. chemical irritants or derivatives thereof. One point of Paul's disclosure is to emphasize that antigen delivery occurred despite the absence of these substances.

Applicant respectfully submits that the substances indicated by the Examiner as relating to element (d) are components of claim 37 element (a), and that Paul et al. does not disclose a composition having element (d) therefore. Applicant respectfully submits that claim 37 is not anticipated by Paul et al. under 35 U.S.C. 102(b), and requests that this rejection be withdrawn.

With regard to claims 38, 40-41, 58-59, and 65, Applicant respectfully these claims are novel at least for the reasons indicated with regard to claim 37, above, and respectfully submits these claims are also novel over Paul et al.

With regard to claims 80-81 and 83-84, Applicant respectfully further submits that Paul does not disclose a composition that is to provide a protective or tolerogenic immune response. With regard to new claims 85 and 86, the claimed compositions are novel because they provide a protective immune response. With regard to new claims 87 and 88, the claimed compositions do not include BSA.

Response to rejection under 35 U.S.C. §103:

In the present Action, claims 37-38, 40-45, 47-48, 50, 55, 58-60, 62-66, 80-84 are rejected under 35 U.S.C. §103(a) as unpatentable over Glenn (WO 98/20734; 1998) in view of Paul (Vaccine Research 4:145-164 (1995)) as set forth in the Office Action mailed May 25, 2006 and, with regard to claim 37 element (d), the Office Action dated January 26, 2009. The rejection states that Glenn discloses all aspects of the present invention except a carrier; that Paul discloses a vaccine using the carrier; and that it would be obvious to one skilled in the art to use Paul's carrier in Glenn's vaccine to take advantage of the carrier's high drug transfer efficacy. The rejection also states there would be a reasonable

expectation of success to combine these two disclosures because Paul discloses that their transfersomes are capable of delivering full size proteins across the skin in a vaccination. Applicant respectfully notes that claim 44 is canceled, and submits the following comments in response to the rejection.

As discussed in part in Glenn, Paul and the present application, the skin is a barrier preventing the entry of external substances through the skin and into the body. Histologically, the skin includes two main layers: the epidermis (outer layer) and the dermis (inner layer). The stratum corneum is the outermost layer of the epidermis, made of layer upon layer of tightly packed, laterally overlapping dead keratinocytes, with tight seals between cells to provide a strong barrier to entry.

In response to the above rejection, Applicant first submits that, while Glenn and Paul both discuss the application of antigenic substances to the skin and measure the systemic immune response (serum antibody concentrations) achieved thereafter, Glenn and Paul together do not teach a transdermal composition/vaccine according to the present invention. Glenn and Paul each teach crossing the stratum corneum using a different system, based on different physiological structures in the stratum corneum.

- Glenn introduces antigens into the stratum corneum via simple diffusion, using peripheral activation of Langerhans cells located there to engulf and process antigen.
- Paul transfers BSA-FITC all the way through the stratum corneum with special penetrants, driven through virtual pores by the skin's water concentration gradient and penetrant's high deformability, and into e.g. the dermis and systemic circulation, to be processed by systemic immune responses.

As all of the pending claims comprise penetrants of the present invention, Applicant submits the present claims are patentably distinct from Glenn in view of Paul. Further details of Glenn and Paul are discussed below.

Glenn's passive diffusion approach discloses that antigens applied to the skin with CT or other bAREs will passively diffuse into the stratum corneum and activate Langerhans cells located there. These activated Langerhans cells take up and process the antigen, and present the antigen to other immune cells. Glenn's composition exploits a body's immune system response for a substance presenton the skin, but that has not gained full access to the body. Glenn does not disclose transport of the antigen itself past the stratum corneum barrier, other than as part of a Langerhans cell. See for instance Glenn page 11 line 5 to page 14 line 21. When discussing an antigen's passive diffusion into the stratum corneum, Glenn notes that the skin barrier is imperfect because Langerhans cells are distributed there, and are able to take up substances including particulate substances and entire microbes. (See e.g. page 11 line 16 to page 13 line 1).

Paul's experiments with BSA-FITC show that larger protein molecules, when associated with highly deformable transfersomes, penetrate the stratum corneum and are delivered to the dermis and systemic bloodstream/ organs (see Paul Figures 1 and 2). Along the way, Paul discloses, associated antigens are presented to the body and induce an immune response comparable to injected antigen. Such penetration is not via simple diffusion, but rather is believed to be driven by both the high deformability of the transfersomes and a transepidermal water concentration gradient, which spontaneously drives tranfersomes and associated materials through virtual pores in the stratum corneum. Langerhans cells in the dermis are along the penetration pathway, Paul notes, which is

convenient since such cells are known to be immunologically dominant in the dermis. Furthermore, immunologically active cells in the skin are believed to be aligned specifically along minute pores in the dermis, to protect these areas from infiltration by e.g. helminths. See for instance Paul Abstract lines 1-11, page 146 3rd and 4th full paragraphs, page 152 1st full paragraph, page 162 3rd-5th full paragraphs.

Given that Paul discloses success in inducing an immune response with penetration/ transfersomes (and expressly discloses no success with simple diffusion), and that Glenn discloses success with simple diffusion, the skilled person would be taught to consider whether they wish to prepare a vaccine based on transfersome penetration of antigen through the stratum corneum for systemic delivery or simple diffusion of antigen into the stratum corneum to be engulfed and processed by Langerhans cells there. Applicant notes that the present claims are directed in part to a penetrant which serves to distinguish the present invention from a simple diffusion system such as Glenn's.

At least in view of the foregoing, Applicant respectfully submits that Glenn does not teach a transdermal delivery system in the context of the present invention. Furthermore, Glenn teaches away from the present invention, teaching that antigen delivery through the stratum corneum is not necessary as simple diffusion to Langerhans cells into the stratum corneum is enough to induce a protective immune response (Example 29).

Second, in response to the present rejection, Applicant respectfully submits that the skilled person would not find it obvious to use Paul's transfersomes in Glenn's vaccine to take advantage of the high drug transfer disclosed in Paul. Specifically, the present rejection states that one skilled in the art would be motivated to combine Glenn and Paul in view of Paul's teaching of $\geq$ 90% drug transfer across the skin using transfersomes.

Applicant respectfully submits that the skilled person, reading Glenn, would not be motivated to combine Glenn and Paul by Paul's teaching of such drug transfer. Antigen transfer via Paul's transfersomes, through the stratum corneum and away from stratum corneum Langerhans cells, would change the principle of operation of Glenn's passive diffusion technique.

At least for the foregoing reasons, Applicant respectfully submits that the skilled person would not find Glenn obvious over the present claims in view of Paul's disclosure of high drug transfer efficacy, and requests that the rejection of these claims be withdrawn.

With regard to the rejection of claim 80 et al. as obvious as indicated above, Applicant further submits that one skilled in the art would not find the subject matter of claims 82-84 obvious in view of Glenn and Paul. As indicated above, Glenn and Paul each teach a different system of transdermal immunization. Glenn Example 29 indicates that a composition disclosed therein provides some protection from a challenge after immunization with its passive diffusion system. Paul's teaching of drug delivery would not teach the skilled person that protection could be achieved via such delivery. As protection had been shown via Glenn, and not shown by Paul, the skilled person would not be taught or motivated to use Paul's drug delivery system to enhance protection taught by Glenn.

Furthermore, Paul teaches that the presence of lipid A or muramyl-dipeptide does not appreciably affect the concentration of immunization-induced anti-BSA molecules, and that this is likely because transfersomes themselves are good immunoadjuvants (See e.g. Abstract lines 19-21, as well as page 159 first full paragraph). According to Paul, immunoadjuvants are only useful for sparsely dosed

(Fig. 4) or the poorly immunogenic hapten FITC. (See also page 162, last paragraph). As indicated in the present Action, within the rejection under 35 USC 112, the development of a protective vaccine is unpredictable. After publishing Paul, further research was conducted and the Applicant surprisingly found that a protective response to TT via the present penetrant-delivery system is only achieved with the presence of a compound that specifically has or induces cytokine activity (or anti-cytokine activity). This is because, while at first it appeared that transfersomes served as their own immunoadjuvant, in fact penetrants of the present invention deliver antigens so gently that cytokine activity must be independently introduced for a protective immune response to begin. See in contrast Paul's comparison of its compositions to helminths, which enter the body through the skin and strongly activate the host's immune system (Paul page 147, 3rd full paragraph). The skilled person would not know, from Paul or Glenn, that the present invention would provide protection only with the inclusion of a compound that e.g. specifically induces cytokine activity. Rather, the skilled person would be taught away from the need for such a compound.

At least for the foregoing reasons, Applicant respectfully submits that the invention of claim 80 et al. is not obvious in view of Glenn and/or Paul, and requests that this rejection be withdrawn therefore.

*****

Applicant respectfully submits that the present Amendment is fully responsive to the pending Action and places the present application in better condition for allowance. Applicant respectfully submits that all pending rejections are overcome and requests that the Examiner allow the application to proceed to grant therefore.

In the event that the Examiner has any questions or concerns regarding this Amendment, the Examiner is invited to contact the below-signed representative by telephone to discuss.

Respectfully submitted,

January 29, 2010
Date

Valerie Neymeyer-Tynkov
Reg. No. 46,956
Neymeyer-Tynkov LLC
20 N. Clark St. Suite 600
Chicago, IL 60602
Phone: 312/965-1969